REMARKS

This paper is responsive to the Office Action dated February 13, 2003, which is the first action on the merits of the application.

Claims 5, 9, 20-28, and 31-34 are pending in the application. Claims 5 and 9 are withdrawn. Claims 21, 22, 24, 25, and 27 are allowed. The other pending claims stand variously rejected. By way of this Amendment, claims 5, 32, 33, and 34 are reworded. The claim count has not changed. No new limitation is added to the amended claims, Accordingly, coverage is maintained for all equivalents of the claimed subject matter for which applicant was previously entitled.

Reconsideration and allowance of the application is respectfully requested.

Declaration

The Office Action indicates that the Declaration previously filed in support of this application pursuant to 37 CFR § 1.67(a) is defective because it claims priority to applications to which applicants have since cancelled their priority claim.

Applicants' representatives are sending a replacement Declaration to the inventors for their signature. It will be filed with the Patent Office when the signatures are obtained.

Claim Objections

Claims 32-34 are objected to for failing to recite the required SEQ. ID NO. By way of this amendment, SEQ. ID NO:2 is now referred to in the claims. Withdrawal of these objections is respectfully requested.

Rejections under 35 USC § 102:

Claim 31 stands rejected under 35 USC § 102(a) as being anticipated by a publication by Nakamura et al. (Science 277:955, 1997). The Office Action indicates that the sequence of human TERT contains within it segments of 10 consecutive amino acids that are identical to segments of 10 consecutive amino acids within the prototype mTERT sequence (SEQ. ID NO:2) claimed in this application.

Applicants respectfully disagree. In order to be claim defeating, the cited prior art must meet all of the claim limitations. Claim 31 covers the following:

An isolated, purified or recombinant polynucleotide encoding a telomerase reverse transcriptase protein, wherein said protein:

(i) has at least 90% sequence identity to SEQ. ID NO:2; and,

(ii) has telomerase catalytic activity when associated with telomerase RNA component;

wherein the polynucleotide encodes a protein that contains at least 10 consecutive amino acids of SEQ. ID NO:2.

As shown in Appendix A attached to this Amendment, full-length human TERT is only about 62% identical to mouse TERT at the amino acid level. The Office Action has not shown how the information provided in the Nakamura reference provides a protein that meets *all* of the required limitations:

- it contains 10 consecutive amino acids of SEQ. ID NO:2;
- it has at least 90% sequence identity to SEQ. ID NO:2; *and*
- it has telomerase catalytic activity when associated with telomerase RNA component.

In particular, the short sequences that are exactly identical between human and mouse TERT are surely not long enough to have telomerase catalytic activity.

Withdrawal of this rejection is respectfully requested.

Claim 28 stands rejected under 35 USC § 102(a) as being anticipated by a patent application by Greider et al. (WO 97/35967). The Office Action indicates that the reference teaches cells and animals that are homozygous mTR knockouts.

Applicants respectfully disagree. mTR is the RNA component of mouse telomerase. mTERT is the protein catalytic component of mouse telomerase. As shown in Appendix B accompanying this amendment, there is no significant sequence homology between the mTR and mTERT sequences. Accordingly, the cited reference does not teach or enable the making of a mouse cell in which an endogenous mTERT gene in the cell has been mutated by recombinant means, or progeny of said cell.

Withdrawal of this rejection is respectfully requested.

Rejection relating to the making of variants:

Claims 20, 23, 26, and 31-34 stand rejected under 35 USC § 112 ¶ 1 on the basis that the specification is not enabled for the making of polynucleotides that encode TERT having at least 90% sequence identity to SEQ. ID NO:2, and having telomerase catalytic activity. The Office Action

indicates that this deficiency will somehow be cured by requiring that the TERT protein contains mouse motifs T, 1, 2, A, B, C, and D.

Applicants respectfully disagree, for reasons already of record in this application. The Office Action indicates that the specification fails to disclose a single polynucleotide sequence that has the required sequence identity and the required function. In fact, the specification discloses the family of sequences that are at least 60% identical to mTERT, of which SEQ. ID NO:2 is exemplary[1,2].

The Office Action refers to *Genentech Inc. v. Novo Nordisk A/s*, USPQ2d 1005 (CAFC 1997) as requiring the specification to supply the novel aspects of an invention in order to constitute adequate enablement. In fact, this application supplies the novel aspect of the invention by providing the sequence of mouse TERT (SEQ. ID NO:2). Based on this prototype sequence, it is a routine matter for the skilled reader to make functional variants that are at least about 90% identical.

The Office Action notes with concern that "the number of possible scenarios increases geometrically with increase in percent non-identity" It cites *In re Wands* (8 USPQ2d 1400, Fed. Cir. 1988) as setting the standard by which someone would be required to undertake "undue experimentation" in order to practice the invention. The Wands patent claims an assay method using an antibody described only as being of the IgM class, and having certain functional properties[3]. Based only upon amino acid sequence, the number of antibody molecules that would fall within the Wands

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[1] Working examples are not required to meet the enablement requirement of § 112 ¶ 1. Nothing more than objective enablement is required, and therefore it is irrelevant whether this teaching is provided though broad terminology or illustrative examples. *In re Wright,* 27 USPQ2d 1510 (Fed. Cir. 1993). The burden is on one challenging validity to show . . that the prophetic examples together with other parts of the specification are not enabling. *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.,* 224 USPQ 409 (Fed. Cir. 1984).

[2] A single illustration is sufficient to show that a broader genus is enabled. "Since one embodiment is. . . disclosed in the specification, along with the general manner in which its current range was ascertained, . . . other permutations of the invention could be practiced by those skilled in the art without undue experimentation." *United States v. Telectronics, Inc.,* 8 USPQ2d 1217 (Fed. Cir. 1988), *cert. denied,* 490 U.S. 1046 (1989).

[3] Claim 1 of U.S. Patent 4,879,219 (J.R. Wands et al.) reads as follows: An immunoassay method utilizing an antibody to assay for a substance comprising hepatitis B-surface antigen (HBsAg) determinants which comprises the steps of: contacting a test sample containing said substance comprising HBsAg determinants with said antibody; and determining the presence of said substance in said sample; wherein said antibody is a monoclonal high affinity IgM antibody having a binding affinity constant for said HBsAg determinants of at least 10^9 M^{-1}.

claim is enormous[4]. Still, the Federal Circuit found that the skilled artisan could obtain other IgM antibodies falling within the claim without undue experimentation — in spite of the considerable number of variant structures from which to chose. Even if only about 2.8% of the hybridomas made according to the description fell within the claim, the Court held that Wands was fully enabled, because it was standard practice to screen negative hybridomas in order to find one that makes the desired antibody[5].

Thus, for the claims under examination in the present application, the proper inquiry is not *how many* possible variants are there that have the specified structure — but whether there are screening methods available at the time of filing that would allow the skilled artisan to obtain variants without undue experimentation that have the required function.

The Office Action cites an article by Lundblad (Proc. Natl. Acad. Sci. USA 95:8415, 1998) as indicating that several conserved motifs are required for telomerase activity. In fact, the article does not indicate that entire motifs are required — only that mutation of particular residues abolishes telomerase activity. The author draws this from the following articles, which are included in the accompanying Information Disclosure Statement:

- Lingner et al., Science 276:561, 1997. Some Asp and Glu residues were changed in *Euplotes* TERT in Motif A, Motif B, and Motif C. Amongst the residues tested, individually changing three of the Asp residues to Ala was found to affect activity. More conservative changes were apparently not tested (or not reported).
- Counter et al., Proc. Natl. Acad. Sci. USA 94:9202, 1997. This paper reports the effect of one change in one residue of Motif A in *Saccharomyces* TERT.
- Weinrich et al., Nat. Genet. 17:498, 1997. Mutations were tested at 15 positions of the human TERT sequence. Nine of these positions could be changed individually without eliminating telomerase activity.

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[4] At least 6.25×10^{82}, using conservative assumptions. This number is derived as follows. Variation between antibody molecules is assumed to occur only in the hypervariable region, about 50 different amino acid positions in both the heavy and light chains. Assume also that there are about 25 variable region genes available for the heavy chain, and about 25 variable region genes available for the κ or λ light chain. Irrespective of function, the number of possible antibody molecules is therefore at least $(50^{20} \times 25)^2 = 6.25 \times 10^{82}$. Of course, only a small proportion of these would meet the binding characteristics of the antibody in the claim. But the required antibody can be obtained without undue experimentation, because functional requirements during immune selection in vivo, and then during hybridoma screening in vitro, drive the process towards production of an antibody molecule with the proper function.

[5] *In re Wands, op. cit.*, 8 USPQ2d at 1406-07.

- Collins et al., Proc. Natl. Acad. Sci. USA 95:8485, 1998. This paper reports testing of a variant of *Tetrahymena* telomerase. Changing both Asp residues in Motif C to Ala was found to affect telomerase activity.

These articles only identify a small collection of variants in which particular changes to particular residues mutations appear to affect telomerase activity. They *don't* establish that the motifs shown in Figure 5 are intolerant to mutations *of any kind.*

Applicants do not deny that variants of the mTERT sequence can be made that lack telomerase function. Such variants are necessarily excluded from the claimed invention as not having the required function. The enablement requirements of § 112 ¶ 1 do not require that *all* possible variants be functional — only that functional variants meeting the other requirements of the claim can be obtained without undue experimentation.

Accompanying this Amendment is a Declaration under 37 CFR § 1.132 by Gregg B. Morin, Ph.D. Dr. Morin explains the following:

- TERT sequences in different eukaryotes can have identities of less than 30%, and yet they perform essentially the same function. Telomerase components appear to be interchangeable between mammalian cells. Yet mouse TERT is only about 64% identical to human TERT at the amino acid level. Thus, considerable variation in the sequence can be accommodated without losing function. Geron's experience with variants and deletion mutants bears this out.
- Motif sequences in DNA polymerase enzymes are known to be highly tolerant to mutations in amino acid sequence. About 42 of the 63 residues in the motif sequences have been changed in the course of evolution of just seven eukaryote TERT proteins. Experimental mutation studies are expected to show even more plasticity.
- It would be easy to construct a library of thousands of TERT variants based on the prototype mouse TERT sequence, using any one of several techniques known in the art at the time this application was filed. The library could then be easily screened using assays described in the specification to identify variants with telomerase activity.

The Declaration by Dr. Morin provides a straightforward protocol by which someone skilled in the art reading the application at the time of filing could use in order to obtain any number of functional TERT variants they require. Employing a random mutagenesis strategy as described, in view of the variability of the motif sequences between natural orthologs, it is expected that some of the

functional variants obtained would have mutations within the motif regions. This is coincidental — there is no reason that someone wanting to make variants that were functional would care particularly where the mutations occurred.

The Declaration reinforces applicants' position that the variants claimed in this application come within the disclosure as filed, based on the *Wands* standard for routine experimentation. Accordingly, the invention as currently claimed meets the enablement requirements of 35 USC § 112 ¶ 1.

To require applicants to put all the motif elements into the claim would unfairly exclude from the literal coverage of this patent a substantial collection of functional variants of mTERT that could be obtained by routine experimentation.

Withdrawal of this rejection is respectfully requested.

Rejection relating to gene therapy

Claim 28 stands rejected under 35 USC § 112 ¶ 2 as containing subject matter not enabled by the specification. The Office Action indicates that the invention falls within the realm of gene therapy, which it maintians is a highly experimental area of research at the present time. It also indicates that the claim encompasses a cell that has been transformed in vivo.

Applicants respectfully disagree that the making of knockout animals was an uncertain art at the present time, or at the time the application was filed. A Keystone Symposium entitled "Knock-in and knock-out. Transgenes, Development and Disease, and sponsored by Genentech and Immunex was held in Tamarron CO on January 12-18, 1991 (New Biol. 3:331, 1991) — over seven years before the filing of this application. A large number of reports have appeared relating to the making of knockout and gene-altered animals (for example, M. Barinaga: "Knockout mice offer first animal model for CF", Science 257:1046, 1992; Harding et al., GenPharm International: "Class switching in human immunoglobulin transgenic mice", Ann. NY Acad. Sci. 764:536, 1995). By the time this application was filed, over 400 papers had been published on knockout mice. Useful references for the altering of endogenous genes by homologous recombination are provided in the specification on page 112, line 13 ff.

The question of enablement therefore depends on these issues: a) does the specification provide the means by which someone skilled in the art of altering genes in mouse cells could specifically target the mouse TERT gene; and b) would targeting the TERT gene somehow compromise the viability of the cell. In fact, the specification provides both the sequence of the cDNA (Figure 4), and of the upstream genomic region (Figure 8). Figure 9 provides an illustration of how an

exemplary targeting vector could be made for removing the translation start sequence, thereby preventing expression of the gene. Page 115 describes the use of such a vector to make a mouse cell having an inactivated endogenous TERT gene.

There is no reason to believe that inactivating or otherwise altering the TERT gene would be lethal to the cell — or to a knockout mouse, for that matter. The patent publication by Greider et al. (WO 97/35967), helpfully provided by the Office in the last Action, establishes that it was already known that mice unable to express telomerase activity are still viable through several generations. The gene inactivated in the Greider publication is the telomerase RNA component, but the RNA component is as essential for telomerase activity as the TERT component. Mice having a homozygously inactivated TERT gene are viable, just as mice having a homozygously inactivated TERT gene are viable. As it happens, there have been no unexpected difficulties in the making of TERT knockout mice, as confirmed in the Declaration previously provided from Dr. Choy Pik Chiu.

With respect to the concern raised in the Office Action that the claim encompasses a cell that has been transformed in vivo: the Office is respectfully reminded that this is a *product* claim, and § 112 ¶ 1 only requires that the specification enable at least one way of making the claimed invention — not all possible ways[6]. In this case, the specification clearly teaches how to make a mouse cell with an altered endogenous TERT gene either by directly targeting the cell in vitro, or by harvesting altered cells from genetically altered mice made by contemporary techniques.

Withdrawal of this rejection is respectfully requested.

Request for Interview

Applicant respectfully requests that all outstanding rejections be reconsidered and withdrawn. The application is believed to be in condition for allowance, and a prompt Notice of Allowance is requested.

In the event that the Examiner determines that there are other matters to be addressed, applicant hereby requests an interview by telephone.

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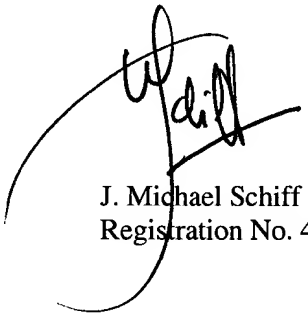
[6] The enablement requirement is met if the description enables any mode of making and using the claimed invention. *Engel Industries, Inc. v. Lockformer Co.*, 20 USPQ2d 1300 (Fed. Cir. 1991).

Fees due

Accompanying this Amendment is a request for a one month extension of time, and an IDS for consideration under 37 CFR § 197(c)(2), along with authorization to charge the Deposit Account with the requisite fees.

No other fee is believed payable for consideration of this paper and the accompanying documents. Nevertheless, should the Patent Office determine that a further extension of time or any other relief is required for further consideration of this application, applicant hereby petitions for such relief, and authorizes the Commissioner to charge the cost of such petitions and other fees due in connection with the filing of these papers to Deposit Account No. 07-1139, referencing the docket number indicated above.

Respectfully submitted,



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